DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Rockville MD 20857

DEC 4 2008

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Re: Docket Nos. FDA-2008-P-0343 and FDA-2008-P-0411

Dear Ms. Wilk-Orescan and Mr. Hurst:

This letter responds to the citizen petition submitted to the Food and Drug Administration (FDA or the Agency) by Novo Nordisk Inc. (Novo Nordisk) on June 9, 2008, and a supplement submitted on July 21, 2008 (Novo Nordisk Petition or Petition). The petition requests that FDA refrain from approving any abbreviated new drug application (ANDA) for a repaglinide product that omits information on metformin combination therapy, which is protected by patent and currently appears in the labeling of the innovator product, Prandin (repaglinide). The Petition contends that the omission of the metformin combination therapy information would render generic versions of Prandin less safe and effective for the remaining, nonprotected conditions of use.

We have carefully reviewed the arguments in the Novo Nordisk Petition. For the reasons stated below, we deny your request.

We are also responding to a related citizen petition submitted to FDA by Winston and Strawn LLP on behalf of Caraco Pharmaceuticals Laboratories, Ltd. (Caraco), on July 14, 2008 (Caraco Petition). The Caraco Petition requests that FDA require any ANDAs for repaglinide that include only a section viii statement for the method-of-use claim of the U.S. Pat. No. 6,677,358 (the '358 patent) for combination therapy with metformin also include a paragraph IV certification to address the other claims of the '358 patent.

We have carefully reviewed the Caraco Petition, and for the reasons below, we grant your request.

FDA-2008-P-0343

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I. BACKGROUND

A. Prandin

On December 22, 1997, FDA approved the new drug application (NDA) held by Novo Nordisk for Prandin (repaglinide) (NDA 20-741). Prandin is currently indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes (non-insulin mellitus). At the time of initial approval, Prandin's indication was described as a monotherapy treatment and for use in combination with metformin. On October 21, 2002, FDA approved a supplement to this NDA that provided for the use of Prandin in combination with thiazolidinediones (TZDs).[1]

In early 2008, FDA reevaluated the labeling for all oral antidiabetic drugs and requested that all oral antidiabetic agents have the following simplified indication: "Drug X is indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus." Pertinent efficacy and safety information from the various clinical trials would still be described in appropriate sections of the label (e.g., CONTRAINDICATIONS, PRECAUTIONS, ADVERSE REACTIONS, Clinical Trials).

In response to this FDA request that all oral antidiabetic drug products have a simplified indication, Novo Nordisk submitted a supplement to the Agency requesting that the Prandin labeling be changed to comply with this directive. Effective July 14, 2008, the labeling for Prandin was revised to exclude specific information in the INDICATIONS AND USAGE section regarding the combination therapy use of this drug product with metformin and TZDs. The newly revised INDICATIONS AND USAGE section reads as follows:

> PRANDIN is indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus.

The data supporting repaglinide monotherapy and combination therapy with metformin or a TZD are derived from separate clinical trials and are described separately in the Prandin labeling.

FDA's *Approved Drug Products with Therapeutic Equivalence Evaluations* (the Orange Book) lists two patents for Prandin: U.S. Pat No. 37,035 (the '035 patent) and the '358 patent. The '035 patent expires on March 14, 2009, and claims, among other things, the

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[1] The INDICATIONS AND USAGE section for the Prandin labeling prior to July 2008 was as follows:

> PRANDIN is indicated as an adjunct to diet and exercise to lower the blood glucose in patients with type 2 diabetes mellitus (NIDDM) whose hyperglycemia cannot be controlled satisfactorily by diet and exercise alone.
> PRANDIN is also indicated for combination therapy use (with metformin or thiazolidinediones) to lower blood glucose in patients whose hyperglycemia cannot be controlled by diet and exercise plus monotherapy with any of the following agents: metformin, sulfonylureas, repaglinide, or thiazolidinediones. . . .

chemical composition of repaglinide. The '358 patent expires on June 12, 2018, and claims, among other things, the use of repaglinide in combination with metformin. Specifically, according to the Novo Nordisk Petition, the '358 patent contains 5 claims: claims 1-3 deal with a pharmaceutical composition containing both repaglinide and metformin; claim 5 concerns a kit comprised of at least repaglinide and metformin; and claim 4, the focus of these petitions, concerns the method of use for the combination of repaglinide and metformin in treating type 2 diabetes (Petition at 3).

B. ANDA for Repaglinide

As explained in the Caraco Petition, Caraco submitted ANDA 77-751 to FDA for repaglinide tablets (0.5 milligram (mg), 1 mg, and 2 mg). The ANDA initially contained a paragraph III certification with respect to the '035 patent and a paragraph IV certification as to the method-of-use claim in the '358 patent. Caraco amended its ANDA in April 2008 to also include a section viii statement (method-of-use statement) to the '358 patent. The section viii statement declares that Caraco is not seeking approval for the method of use claimed by the '358 patent (i.e., that it is not seeking the approval for the method of use for the repaglinide/metformin combination therapy).

C. The Statutory and Regulatory Basis for Patent Protection for NDAs and for Labeling Differences for ANDAs

The Federal Food, Drug and Cosmetic Act (the Act) and FDA regulations require that a sponsor seeking to market an innovator drug submit an NDA. NDAs contain, among other things, extensive scientific data demonstrating the safety and effectiveness of the drug for the indication for which approval is sought. The Act and FDA regulations also require that a sponsor of an NDA submit to FDA a list of patents claiming the approved drug substance or drug product, or claiming an approved method of using the drug product described in the NDA. Specifically, section 505(b)(1) of the Act (21 U.S.C. 355(b)(1)) requires NDA applicants to file as part of the NDA "the patent number and the expiration date of any patent which claims the drug for which the applicant submitted the application or *which claims a method of using such drug* and with respect to which a claim of patent infringement could reasonably be asserted if a person not licensed by the owner engaged in the manufacture, use, or sale of the drug" (emphasis added).[2] FDA is required to publish patent information for drugs approved under section 505(c) and does so in the Orange Book (section 505(b)(1), (c)(2), and (j)(7) of the Act and 21 CFR 314.53(e)).

A drug product with an effective approval under section 505(c) of the Act is known as a *listed drug*.[3] Under provisions added to the Act by the 1984 Drug Price Competition and

[2] Section 505(c)(2) of the Act imposes an additional patent submission requirement on holders of approved NDAs when those holders subsequently obtain new patent information that could not have been submitted with the NDA.

[3] Under 21 CFR 314.3(b), "[*l*]*isted drug* means a new drug product that has an effective approval under section 505(c) of the act for safety and effectiveness or under section 505(j) of the act, which has not been withdrawn or suspended under section 505(e)(1) through (e)(5) or (j)(5) of the act, and which has not been

Patent Term Restoration Act (Hatch-Waxman Amendments), Public Law No. 98-417, 98 Stat. 1585, the Act permits submission of ANDAs for approval of generic versions of listed drugs (see section 505(j) of the Act). The ANDA process shortens the time and effort needed for approval by, among other things, allowing an ANDA applicant to rely on FDA's previous finding of safety and effectiveness for a listed drug rather than requiring the ANDA applicant to independently demonstrate the safety and effectiveness of its proposed drug. To rely on such a finding, the ANDA applicant must show that its proposed drug product is the same as the listed drug in many respects (including active ingredient, dosage form, strength, route of administration, and, with certain narrow exceptions, labeling), and that its product is bioequivalent to the listed drug.

Each ANDA applicant must identify the listed drug on which it seeks to rely for approval. As described in more detail below, the timing of ANDA approval depends on, among other things, the intellectual property protections for the listed drug the ANDA references and whether the ANDA applicant challenges those protections (see section 505(b), (c), (j)(2)(A)(vii), and (j)(5)(B) of the Act).[4] In general, an ANDA may not obtain final approval until listed patents and marketing exclusivity have expired or until NDA holders and patent owners have had the opportunity to defend relevant patent rights in court.

Specifically, with respect to each patent submitted by the sponsor for the listed drug and listed in the Orange Book, the ANDA applicant generally must submit to FDA one of four specified certifications under section 505(j)(2)(A)(vii) of the Act. The certification must state one of the following:

(I) That the required patent information relating to such patent has not been filed (paragraph I certification)
(II) That such patent has expired (paragraph II certification)
(III) That the patent will expire on a particular date (paragraph III certification)
(IV) That such patent is invalid or will not be infringed by the drug for which approval is being sought (paragraph IV certification)

The purpose of these certifications is "to give notice, if necessary, to the patent holder so that any legal disputes regarding the scope of the patent and the possibility of infringement can be resolved as quickly as possible" (*Torpharm, Inc. v. Thompson*, 260 F. Supp. 2d 69, 71 (D.D.C. 2003)).

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withdrawn from sale for what FDA has determined are reasons of safety or effectiveness." A listed drug is identified as having an effective approval in the Orange Book, which includes patent information for each approved drug (§ 314.53(e)).

[4] Relevant intellectual property protections affecting the timing of ANDA approval include marketing exclusivity and listed patent protection for the listed drug. Marketing exclusivity is not at issue here, so this response does not address the effect of exclusivity on ANDA approval but focuses, instead, on relevant patent protection.

If an applicant files a paragraph I or II certification, the patent in question will not delay ANDA approval. If an applicant files a paragraph III certification, the applicant agrees to wait until the relevant patent has expired before seeking full effective approval of its ANDA.

If, however, an applicant wishes to seek approval of its ANDA before a listed patent has expired by challenging the validity of a patent or claiming that a patent would not be infringed by the product proposed in the ANDA, the applicant must submit a paragraph IV certification to FDA. The applicant filing a paragraph IV certification must also provide a notice to the NDA holder and the patent owner stating that the application has been submitted and explaining the factual and legal bases for the applicant's opinion that the patent is invalid or not infringed (see section 505(b)(2)(B) and (j)(2)(B) of the Act).

The filing of a paragraph IV certification "for a drug claimed in a patent or the use of which is claimed in a patent" is an act of patent infringement (35 U.S.C. 271(e)(2)(A)). If the patent owner or NDA holder brings a patent infringement suit against the ANDA applicant within 45 days of the date it received notice of the paragraph IV certification, the approval of the ANDA will be stayed for 30 months from the date of such receipt by the patent owner and NDA holder, unless a court decision is reached earlier in the patent case or the patent court otherwise orders a longer or shorter period (see section 505(c)(3)(C) and (j)(5)(B)(iii) of the Act). When the 30 months have expired, the patent ceases to be a barrier to final ANDA approval, even if the patent litigation is ongoing. Similarly, if the NDA holder and patent owner receive notice of a paragraph IV certification and decline to sue within 45 days of receipt of notice, the patent will not be a barrier to ANDA approval.

These paragraph I, II, III, and IV certifications are not the only manner in which an ANDA applicant may address all relevant patents. When a patent is listed only for a method of use, an ANDA applicant seeking to omit that approved method of use covered by the listed patent need not file a paragraph I to IV certification for that patent. Instead, the applicant may submit a *section viii statement* acknowledging that a given method-of-use patent has been listed, but stating that the patent at issue does not claim a use for which the applicant seeks approval (see section 505(j)(2)(A)(viii) of the Act). Specifically, section 505(j)(2)(A)(viii) of the Act provides that "if with respect to the listed drug referred to in [section 505(j)(2)(A)(i)] information was filed under subsection (b) or (c) for a method of use patent which does not claim a use for which the applicant is seeking approval under this subsection, [the ANDA must contain] a statement that the method of use patent does not claim such a use." Such a statement requires the ANDA applicant to omit from its labeling information pertaining to the protected use (21 CFR 314.92(a)(1) and 314.94(a)(12)(iii)). If an ANDA applicant files a section viii statement, the patent claiming the protected method of use will not serve as a barrier to ANDA approval.[5]

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[5] See also H.R. Rep. No. 857 (Part I), 98th Cong., 2d sess. 21.

> . . .The [ANDA] applicant need not seek approval for all of the indications for which the listed drug has been approved. For example, if the listed drug has

FDA implementing regulations at § 314.94(a)(12)(iii) describe the applicability of the section viii statement. Section 314.94(a)(12)(iii) states:

> If patent information is submitted under section 505(b) or (c) of the [A]ct and § 314.53 for a patent claiming a method of using the listed drug, and the labeling for the drug product for which the applicant is seeking approval does not include any indications that are covered by the use patent, [the ANDA applicant must submit] a statement explaining that the method of use patent does not claim any of the proposed indications.[6]

Accordingly, FDA regulations also expressly recognize that by submitting a section viii statement, an ANDA applicant may omit from the proposed labeling a method of use protected by a listed patent, and therefore need not seek approval for that use.[7]

The right to file a section viii statement and carve out from labeling method-of-use information protected by a patent has been upheld by the courts. Thus, in *Purepac Pharmaceutical Company v. Thompson*, 354 F.3d 877 (D.C. Cir. 2004), the D.C. Circuit stated that a "section viii statement indicates that a patent poses no bar to approval of an ANDA because the applicant seeks to market the drug for a use other than the one encompassed by the patent" (id. at 880). Similarly, in *Torpharm*, 260 F. Supp. 2d at 73, the D.C. District Court stated that a section viii statement "avers that the patent in

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> been approved for hypertension and angina pectoris, and if the indication for hypertension is protected by patent, then the applicant could seek approval for only the angina pectoris indication.

[6] FDA regulations implementing this statutory provision use the term *indications* to refer to information an ANDA applicant omits from its labeling in the context of submitting a statement that a protected use of a drug is not claimed in a listed patent (§ 314.94(a)(12)(iii)). However, the preambles for the proposed rule and final rule on patent and exclusivity provisions related to ANDA approval express no intent to distinguish between method of use and indication, using the terms interchangeably (see, e.g., 59 FR 50338 at 50347 (October 3, 1994)). Moreover, the preamble to the final rule emphasizes that an ANDA applicant does not have the option of choosing between a paragraph IV certification and a section viii statement where the patent claims only a method of use; where the labeling does not include the indication, only the section viii statement is appropriate (id.). The preamble to the proposed rule states that where "the labeling for the applicant's proposed drug product does not include any indications that are covered by the use patent," the ANDA applicant would submit a section viii statement rather than a paragraph IV certification (54 FR 28872 at 28886 (July 10, 1989)).

[7] See also the final rule, Applications for FDA Approval to Market a New Drug: Patent Submission and Listing Requirements and Application of 30-Month Stays on Approval of Abbreviated New Drug Applications Certifying That a Patent Claiming a Drug Is Invalid or Will Not Be Infringed (68 FR 36676 (June 18, 2003)). In the preamble to this final rule, we stated that the section viii statement permits an ANDA applicant to "avoid certifying to a patent by stating that it is not seeking approval for the use claimed in the listed patent" (68 FR 36676 at 36682). We stated, "[o]ur position has been that, for an ANDA applicant to file a section viii statement, it must 'carve-out' from the proposed ANDA labeling, the labeling protected by the listed patent" (id.).

question has been listed, but does not claim a use for which the applicant seeks FDA approval." These courts have upheld the Agency's interpretation that an ANDA applicant may choose not to seek approval for a method of use protected by a listed patent, and under those circumstances, that patent will not be a barrier to ANDA approval.

Thus, under the procedures established in the Hatch-Waxman Amendments, an ANDA will not be approved until all listed patents (1) have expired, (2) have been successfully challenged, (3) have been subject to a paragraph IV certification pursuant to which the patent owner or NDA holder has declined to sue within 45 days, (4) have been subject to a paragraph IV certification that led to a lawsuit and either a decision favorable to the ANDA applicant or a 30-month stay that has since expired, or (5) are subject to a section viii statement and a corresponding labeling carve-out.

D. Requirements Regarding ANDA Labeling

Section 505(j)(2)(A)(i) of the Act requires that an ANDA contain "information to show that the conditions of use prescribed, recommended, or suggested in the labeling proposed for the new drug have been previously approved for a [listed drug]." This language reflects Congress's intent that the generic drug be safe and effective for each "condition of use" prescribed, recommended, or suggested in the generic drug labeling. However, it does not require that an ANDA be approved for each condition of use for which the reference listed drug is approved. Thus, in § 314.92(a)(1), FDA has explicitly stated that a proposed generic drug product must have the same conditions of use as the listed drug, "except that conditions of use for which approval cannot be granted because of . . . an existing *patent* may be omitted" (emphasis added).

The Act also requires that an ANDA contain "information to show that the labeling proposed for the new [generic] drug is the same as the labeling approved for the listed drug. . . except for changes required because of differences approved under a petition filed under [section 505(j)(2)(C) of the Act] or because the new drug and the listed drug are produced or distributed by different manufacturers" (section 505(j)(2)(A)(v) of the Act). A parallel provision appears in section 505(j)(4)(G) of the Act. [8]

Similarly, the regulations at § 314.94(a)(8)(iv) require the following:

> Labeling (including the container label, package insert, and, if applicable, Medication Guide) proposed for the [generic] drug product must be the same as the labeling approved for the reference listed drug, except for changes required because of differences approved under a petition filed under § 314.93 [21 CFR 314.93] or because the drug product and the reference listed drug are produced or

[8] Section 505(j)(4)(G) of the Act provides that FDA must approve an ANDA unless, among other things, the "information submitted in the application is insufficient to show that the labeling proposed for the drug is the same as the labeling approved for [the reference listed drug] except for changes required because of differences approved under [an ANDA suitability petition] or because the drug and the listed drug are produced or distributed by different manufacturers."

distributed by different manufacturers.

Section 314.94(a)(8)(iv) sets forth examples of permissible differences in labeling that may result because the generic drug product and reference listed drug are produced or distributed by different manufacturers. These differences include the following:

> . . . differences in expiration date, formulation, bioavailability, or pharmacokinetics, labeling revisions made to comply with current FDA labeling guidelines or other guidance, or *omission of an indication or other aspect of labeling protected by patent* [emphasis added] or accorded exclusivity under section 505(j)(4)(D) of the [A]ct.[9]

The regulations at 21 CFR 314.127(a)(7) further provide that to approve an ANDA containing proposed labeling that omits "aspects of the listed drug's labeling [because those aspects] are *protected by patent* [emphasis added]," we must find that the "differences do not render the proposed drug product less safe or effective than the listed drug for all remaining non-protected conditions of use."

Relevant case law affirms an ANDA applicant's ability to carve out protected labeling without violating the "same labeling" requirement. For example, in *Bristol-Myers Squibb v. Shalala*, 91 F.3d 1493, 1500 (D.C. Cir. 1996), the D.C. Circuit ruled that "the statute expresses the legislature's concern that the new generic be safe and effective for each indication that will appear on its label; whether the label for the new generic lists every indication approved for the use of the pioneer is a matter of indifference." Similarly, in *Sigma-Tau Pharmaceuticals, Inc. v. Schwetz*, 288 F.3d 141, 148, fn. 3 (4th Cir. 2002), the Fourth Circuit upheld the right of an ANDA applicant to carve out an indication protected by orphan drug exclusivity as a permissible difference due to difference in manufacturer. Thus, under the statute, regulations, and applicable case law, the carve-out of patent-protected labeling is generally permitted as a permissible difference due to difference in manufacturer if the omission does not render the proposed drug product less safe or effective for the conditions of use that remain in the labeling.

II. ANALYSIS OF THE NOVO NORDISK PETITION

In your Petition, you state that at least one ANDA applicant, Caraco, has received tentative approval for a generic version of repaglinide (Petition at 2). You state that Caraco's proposed labeling for a generic repaglinide omits the information regarding metformin combination therapy. You argue that labeling omitting the metformin combination therapy information would result in insufficient and misleading information to physicians prescribing the drug product, the pharmacists dispensing the drug, and patients using the drug (Petition at 2).

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[9] We note that, due to a series of amendments to the Act, the reference in § 314.94(a)(8)(iv) to section 505(j)(4)(D) of the Act corresponds to current section 505(j)(5)(F) of the Act.

On a number of occasions, we have affirmed our authority to approve generic drug products with carved-out labeling. For example, in our response to the citizen petition concerning ANDAs for ribavirin,[10] we affirmed our authority to approve generic ribavirin drug products with labeling that omits protected information and rejected arguments similar to the ones you raise here. We reiterated this position recently in our response to a citizen petition concerning ANDAs for amifostine with a protected indication carved out;[11] in our response to a citizen petition concerning ANDAs for dronabinol;[12] and in our response to a citizen petition concerning ANDAs for ramipril.[13] In addition, in our response to a citizen petition concerning irinotecan,[14] we rejected the petitioner's arguments regarding carved-out labeling for that drug product when used in combination with another drug product, stating that we would allow ANDAs for irinotecan to omit from their labeling information on the use of the drug in combination with 5-fluorouracil and leucovorin because such omission did not render the drug less safe or effective for the remaining non-protected conditions of use.

A. A Section viii Statement Is Appropriate for the '358 Patent.

You state that a section viii statement, with respect to the '358 patent, is inappropriate because the ANDA applicant is seeking approval to market the drug product for a limited subset of all uses for which the reference drug has been approved (Petition at 5). You claim that in accordance with an FDA directive for all oral antidiabetic drugs, the proposed revised labeling for Prandin will only contain a single indication for Prandin. You also claim that because the Prandin labeling has only one indication, there is no additional indication or use that can be carved out by a section viii statement (Petition at 6). We disagree that a section viii statement, with respect to the '358 patent, is inappropriate.

As explained in section I.A, the Prandin labeling currently contains only 1 indication: as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes. We disagree, however, with your conclusions that a section viii statement is inappropriate because there is not a separate combination indication to carve out or because use in combination with metformin was approved at the time of the initial NDA approval. The statute and regulations do not require a separate indication for a carve-out. Section 505(j)(2)(A)(viii) of the Act refers to "a use" for which the applicant is seeking approval.

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[10] April 6, 2004, letter from Steven K. Galson, Acting Director, Center for Drug Evaluation and Research, to David M. Fox, Docket No. 2003P-0321/CP1 (Ribavirin Response Letter).

[11] March 13, 2008, letter from Janet Woodcock, Director, Center for Drug Evaluation and Research, to William C. Bertrand, Jr., Docket No. 2006P-0410/CP1 (Amifostine Response Letter).

[12] April 25, 2008, letter from Janet Woodcock, Director, Center for Drug Evaluation and Research, to Victor Raczkowski, M.D., Docket No. FDA-2007-P-0169 (Dronabinol Response Letter).

[13] June 18, 2008, letter from Janet Woodcock, Director, Center for Drug Evaluation and Research, to Thomas K. Rogers, Docket No. FDA-2008-P-0304 (Ramipril Response Letter).

[14] July 28, 2008, letter from Janet Woodcock, Director, Center for Drug Evaluation and Research, to Ernest Lengle, Ph.D., Docket No. FDA-2008-P-0069 (Irinotecan Response Letter).

Although the regulations refer to the term indication, FDA has expressed no intent to distinguish between method of use and indications (see footnote 6). In fact, FDA has permitted the carve-out of methods of use that are not a separate indication in several of the examples cited in your Petition (see, e.g., tramadol, oxandrolone). Specifically, in tramadol, we concluded that we need not resolve the issue of whether tramadol is approved for only a single indication (the treatment of moderate to moderately severe pain) or is separately indicated for chronic and acute pain where portions of tramadol's labeling relating to a 50 mg, 16-day titrating regimen are not protected by patent and the requirements of 21 CFR 314.127(a)(7) are met.[15] Similarly, in oxandrolone, we concluded that geriatric labeling regarding oxandrolone's indication for weight gain that is protected by exclusivity could be omitted from the labeling of generic products.[16] We have permitted carve-outs in the context of both geriatric and, as discussed below, pediatric labeling. As explained in section II.B, a carve-out of the metformin combination data will not render the product less safe or less effective for the remaining conditions of use, as there will be no impact on the data from the clinical trials supporting the use of repaglinide as monotherapy or in combination therapy with a TZD.

B. A Split Certification Is Appropriate Because the '358 Patent Contains Composition Claims, a Product Claim, and a Method-of-Use Claim.

You also assert that allowing a split certification (a paragraph IV certification and section viii statement) with respect to a single patent appears to run counter to FDA practice. We disagree.

FDA's practice is to allow both a paragraph IV certification and a section viii statement to the same patent when the patent claims both the drug (or an aspect of the drug such as the formulation or drug delivery system) and a method of using the drug. When the patent contains multiple claims, as is the case with Prandin, the ANDA applicant may file a paragraph IV certification to some claims and a section viii statement to other claims.

The Agency has previously explained that a paragraph IV certification and a section viii statement "are not overlapping, and an applicant does not have the option of making a certification under § 314.94(a)(12)(i)(A)(4) in lieu of, or in addition to, a statement under § 314.94(a)(12)(iii)" (see final rule, Abbreviated New Drug Application Regulations; Patent and Exclusivity Provisions (59 FR 50338 at 50347 (October 3, 1994)). The Agency further noted (at 50347):

> If, however, there are listed patents that present both a product and method of use claim, the applicant may file a paragraph IV certification with respect to the product patent or patent claim and a statement that the product that is the subject

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[15] June 11, 2002, letter from Janet Woodcock, Director, Center for Drug Evaluation and Research, to Ms. Macdonald, Ms. Jaskot, and Mr. Hurst, Docket Nos. 2001P-0495, 2002P-0191, and 2002P-0252 (Tramadol Response Letter).

[16] December 1, 2006, letter from Steven K. Galson, Director, Center for Drug Evaluation and Research, to Edward John Allera, Docket No. FDA-2005-P-0383 (Oxandrolone Response Letter).

of the application does not involve a patented method of use with respect to the method of use patent or patent claim.

In support of your position (Petition at 4, n.8), you quote the *Purepac* decision as stating that there is a long-standing rule that for every patent, only one of two approaches — a section viii statement or a paragraph IV certification — is appropriate (Petition at 4, n.8). The *Purepac* case involved the drug gabapentin, approved to treat epilepsy, and U.S. Patent No. 5,084,479 (the '479 patent) that was listed in the Orange Book. The '479 patent was a method-of-use patent for treating neurodegenerative diseases, which was an unapproved use of gabapentin. Purepac submitted an ANDA for gabapentin and filed a section viii statement to the '479 patent because Purepac was not seeking approval to market gabapentin for the treatment of neurodegenerative disease (Id. at 881). FDA informed Purepac that a paragraph IV certification to the '479 patent should have been submitted because the owner of the reference listed drug product claimed that the "patent covered gabapentin's use for treating epilepsy." Purepac refused to file a paragraph IV certification in place of its section viii statement to the '479 patent and sued FDA. The district court held that the "FDA should have concluded ... that the '479 patent covered gabapentin's use for treating neurodegenerative diseases" and since "Purepac sought approval for a different use ... the district court directed FDA to accept the company's section viii statement" (Id. at 881-82).

Your reliance on the *Purepac* case to support your position on repaglinide is not persuasive because gabapentin did not involve a patent that contained multiple claims for a drug substance and a method of use. At issue in the *Purepac* case was whether a paragraph IV or a section viii statement was appropriate for the method-of-use '479 patent. A combination patent with multiple claims can be evaluated claim by claim, with a paragraph IV certification being applicable to some claims and a section viii statement being applicable to other claims. A section viii statement is appropriate when a patent listed in the Orange Book "[claims] a method of using the listed drug, and the labeling for the drug product for which the applicant is seeking approval does not include any indications that are covered by the use patent" (21 CFR 314.94(a)(12)(iii)(A)). The '358 patent for Prandin is a combination patent that claims both a drug and a method of using the drug in combination with metformin. Therefore, the correct approach for Caraco to address the '358 patent would be a paragraph IV certification to claims covering the drug (claims 1-3 and 5) and a section viii statement for the claim covering the method of using the drug (claim 4) to obtain approval for the use of repaglinide as a monotherapy treatment and as a combination therapy with TZDs.

Furthermore, FDA has permitted applicants to split certifications where a single patent contains claims either for a drug substance or drug product and a method of use or for multiple methods of use. FDA has a consistent practice of permitting other ANDA applicants to submit applications containing both a paragraph IV certification and a section viii statement to the same patent. For example, in Mylan Pharmaceuticals Inc.'s (Mylan's) ANDA 78-902 for Paroxetine Tablets, Mylan filed a paragraph III certification to U.S. Patent No. 4,721,723 and a paragraph IV certification to U.S. Patent Nos. 5,872,132, 5,900,423, 6,113,944, 6,133,289, and 6,121,291 (the '291 patent) (claim 2). A section viii statement was also filed for the '291 patent (claim 1). The Agency permitted

Mylan to carve out the labeling protected by claim 2 of the '291 patent (with a section viii statement) while simultaneously challenging another method of use claim protected by the other claims of the patent. Similarly, in Barr Laboratories, Inc.'s (Barr's) ANDA for fluoxetine hydrochloride, U.S. Patent No. 4,626,549 was listed in the Orange Book as covering more than one claim described by the NDA holder as covering different uses of fluoxetine hydrochloride. The Agency indicated that it would permit ANDA applicants to file a paragraph IV certification to the '549 patent to assert that the labeling does not infringe the patent or that the patent is invalid or unenforceable for some of the claims and also include a section viii statement to indicate that the method of use claim does not claim a use for which the ANDA applicants are seeking approval. Just as the Agency has accepted both a paragraph IV certification and a section viii statement for the same patent in the past where it claims both the drug product and an approved method of using the drug, it is acceptable for Caraco to submit both a paragraph IV certification and a section viii statement for the '358 patent.

C. Omission of the Protected Indication From the Labeling of Generic Versions of Repaglinide Does Not Render Repaglinide Less Safe and Effective for the Remaining, Nonprotected Conditions of Use.

You claim that if the information on the use of repaglinide in combination with metformin is omitted from the labeling, this drug will be less safe and effective for the remaining conditions of use (Petition at 6-11). You state that the combination therapy statement in the product labeling is crucial information, especially since repaglinide is increasingly used in combination with metformin (Petition at 8-9). You state that omitting this information ignores the progressive nature of type 2 diabetes and would give a false impression that the two drugs should not be used in combination with each other (Petition at 10). In addition, you claim that the omission of the metformin information would imply that the only approved combination therapy would be the use of repaglinide with TZDs (Petition at 10). You state that there are a number of warnings or precautions associated with TZDs that are not present with metformin. Consequently, you claim that safety would be compromised because of the absence of labeling for metformin combination therapy. Furthermore, you argue that removal of the metformin combination, which may involve lower initial does of metformin than when metformin is used as monotherapy, would result in higher dosages of metformin when taken as a monotherapy, resulting in a higher incidence of side effects (Petition at 11). Last, you state that eliminating the data and information pertaining to the safe use of repaglinide in combination with metformin eliminates the safe and effective use of repaglinide in combination with both metformin and a TZD (Petition at 11).

As noted in section I.D above, an ANDA may be approved after omitting a patent-protected condition of use if omission of the protected information does not render the application less safe or effective for the remaining, *nonprotected* conditions of use. FDA has concluded that when information regarding the combination use of repaglinide with metformin is carved out, generic repaglinide will remain safe and effective for the remaining, nonprotected conditions of use.

When information relating to the protected, metformin combination therapy use is removed from the repaglinide labeling, the information that will appear in the generic labeling will be the information regarding the nonprotected monotherapy and combination therapy with TZDs. As mentioned in section I.A above, Novo Nordisk submitted a supplement to the Agency requesting that the Prandin labeling be changed to comply with FDA's request that all anti-diabetic drug products have a simplified indication. Effective July 14, 2008, the labeling for Prandin was revised to exclude information in the INDICATIONS AND USAGE section regarding the combination therapy use of this drug product with metformin and TZDs. As such, the INDICATIONS AND USAGE section for the generic repaglinide labeling will be identical to Prandin. Only the references to metformin combination therapy in other sections of the drug labeling will be carved out from the generic product's labeling. The remaining metformin information is contained in the CLINICAL PHARMACOLOGY section under Clinical Trials and the DOSAGE AND ADMINISTRATION section of Prandin's labeling. We have determined that carving out the metformin information in these sections of the drug labeling will not render the product less safe or effective for the remaining, nonprotected conditions of use.

The only trial described in the labeling that involved the combination of Prandin and metformin was a small trial comparing this combination to each of the monotherapies. Only 27 patients in that study received Prandin plus metformin. Despite these small numbers, the contribution of efficacy that Prandin makes to the combination of Prandin plus metformin is comparable to Prandin monotherapy. Furthermore, if a patient needs combination therapy with metformin, that patient can take the innovator drug, consistent with Prandin's labeling. In addition, no safety data from the Prandin plus metformin trial were included in the innovator label. Thus, a carve-out of the metformin combination study results will not render the product less safe or less effective for the remaining uses.

In addition, there is sufficient safety information that will remain in the labeling after the carve-out of the metformin information. In fact, the safety information pertaining to the use of Prandin as monotherapy and in combination with TZDs is not affected by the carve-out of the metformin information because it was derived from different clinical trials. For example, the information regarding safety issues involving hypoglycemia will remain in the Prandin labeling.[17] In addition, the safety data in the Prandin label regarding the risk of serious cardiovascular events will remain after a carve-out because these data were not derived from the metformin combination therapy trials.

As mentioned above, you state that omitting the information on repaglinide and metformin coadministration ignores the progressive nature of type 2 diabetes. Progression of type 2 diabetes is well known with most patients requiring coadministration of multiple antidiabetic therapies over time, and the labeling will provide information about the use of repaglinide with TZDs. As previously mentioned, if

[17] Hypoglycemia has been known for many years to be a risk with the use of sulfonylureas and insulin, and this information is included in the labels for these products. Because Prandin and the sulfonylureas have a similar mechanism of action, similar language regarding hypoglycemia was inserted into the Prandin label when Prandin was approved in 1997.

a patient needs combination therapy with metformin, that patient can take the innovator drug, consistent with Prandin's labeling. In fact, a joint consensus statement from the American Diabetes Association and European Association for the Study of Diabetes in December 2008 (consensus statement) maintains that "more than one medication will be necessary for the majority of patients over time."[18] The consensus statement further explains why most patients should be treated with metformin initially and that insulin or an insulin secretagog (like repaglinide) should be added later.

We reject your claim that a repaglinide drug product labeling containing only the TZD combination therapy would render the drug product less safe than Prandin. As noted previously in section II.A, FDA has reevaluated the labeling for all oral antidiabetic drugs and has eliminated the terms monotherapy and combination therapy from the INDICATIONS AND USAGE section. The recently revised label states that Prandin is indicated as an adjunct to diet and exercise to improve glycemic control in patients with type 2 diabetes. The presence or absence of metformin information in the Clinical Trials section should have no impact on how repaglinide is used as monotherapy or in combination with a TZD. Dosing of all oral antidiabetic agents is based on findings of efficacy and tolerability in individual patients, and medications such as metformin and repaglinide are titrated based on clinical effect. Furthermore, the efficacy and safety data from repaglinide and TZD coadministration will be retained in the repaglinide label, ensuring safe and effective use of these coadministered products.

In addition, we do not believe that the absence of labeling for metformin combination therapy would result in higher dosages of metformin when taken as a monotherapy, resulting in a higher incidence of side effects. As explained above, dosing of all oral antidiabetic agents is based on findings of efficacy and tolerability in individual patients, and medications such as metformin are titrated based on clinical effect. In addition, the consensus statement contains a box insert called the "Titration of Metformin" with recommendations that are different from the label of metformin-containing products.[19] The consensus statement recommends a starting dose as low as 500 mg metformin once daily (the lowest dose in the label is 500 mg twice daily or 850 mg once daily), followed with titration every 5-7 days (the label says every two weeks). The consensus statement also recommends that patients decrease the dose for gastrointestinal symptoms but try to advance the dose at a later time.

D. FDA's Recent Responses to Citizen Petitions on a Carve-Out Issue Do Not Require That FDA Grant Your Request.

You claim that FDA's response to several recent citizen petitions regarding carve-out issues requires FDA to grant your request (Petition at 11-14). We disagree.

Our approval of an ANDA for repaglinide without information on metformin combination use would be consistent with our approvals of other generic drug products

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[18] Nathan, D, et. al.: Medical Management of Hyperglycemia in Type 2 Diabetes: A Consensus Algorithm for the Initiation and Adjustment of Therapy. *Diabetes Care* 31:1-11, 2008, p.8.
[19] Id., page 7.

with carved-out indications and conditions of use. For example, in *Bristol-Myers Squibb*, we approved generic captopril with labeling that excluded two protected indications and corresponding protected, indication-specific dosing information. We did so even though the dosing and administration for the approved generic use was twice as high as the dosing for the carved-out indication. The D.C. Circuit held that omission of the indications protected by exclusivity was a difference in labeling "required . . . because the drug and the listed drug are produced or distributed by different manufacturers" within the meaning of the Act (91 F.3d at 1500).

Many of FDA's recent responses to citizen petitions either can be distinguished from the Prandin carve-out situation or support the carve-out of the metformin combination therapy information because the drug product would still be safe and effective for the remaining conditions of use. For example, the citizen petition involving Rapamune (sirolimus)[20] requested that FDA refrain from approving ANDAs for sirolimus that omitted information regarding cyclosporine withdrawal from the drug product labeling before the expiration of exclusivity for the protected information. Rapamune was originally approved for use in combination with cyclosporine and corticosteroids. It was later determined that the combination of Rapamune and cyclosporine was associated with the risk of increased renal function impairment. A clinical study was performed which determined that the benefits of withdrawing cyclosporine outweighed risks of immune system reactions. The Agency determined that the inclusion of the cyclosporine withdrawal information was necessary for the safe and effective use of the drug. The carve-out described in the Rapamune Response Letter is significantly different from your Prandin petition because we have determined that Prandin can be safely used for its remaining conditions of use as a monotherapy and as combination therapy with TZDs.

You claim that the rationale in the citizen petition for oxandrolone[21] permitting a carve-out of the geriatric information cannot be applied to the situation involving Prandin (Petition at 12-13). The citizen petition for oxandrolone requested that the Agency refuse to approve any ANDAs for oxandrolone until the exclusivity for geriatric use expired. The petitioner for oxandrolone argued that the geriatric use information in the labeling could not be omitted because this information was necessary to ensure the safe and effective use of the drug product. You argue that the Oxandrolone Response Letter differs from Prandin because the information carved out of the generic oxandrolone labeling was simultaneously applicable to the geriatric and non-geriatric patient population (Petition at 13). With the Prandin labeling, you argue, the information proposed to be deleted from the labeling for generic versions of the drug product is not applicable to the entire repaglinide patient population all the time (Petition at 13). Furthermore, you distinguish the two situations by stating that oxandrolone had been marketed for more than 40 years without the recently added geriatric information,

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[20] See the September 20, 2004, letter from Steven K. Galson, Acting Director, Center for Drug Evaluation and Research, to Mr. Labson and Ms. Walsh, Docket No. (2003P-0518) (Rapamune Response Letter).

[21] See the December 1, 2006, letter from Steven K. Galson, Director, Center for Drug Evaluation and Research, to Mr. Allera and Mr. Sullivan, Docket No. 2005P-0383 (Oxandrolone Response Letter).

whereas, the Prandin product labeling has always contained the metformin information since approval by FDA.

In the Oxandrolone Response Letter, the Agency determined that the safety and effectiveness information for the geriatric use was also contained in other parts of the labeling; therefore, omission of the geriatric information would not render the drug less safe or effective. Similarly, we have determined that the omission of the metformin information in the labeling for generic repaglinide would not render the drug product less safe or effective for the remaining conditions of use. Even though the metformin information in the repaglinide labeling applies to different patient populations at different times and has been included in the product labeling since it has been on the market, we have determined that the information that remains in the labeling after the metformin information is carved out is sufficient for its safe and effective use and does not render the product less safe or effective for the remaining conditions of use (see section II.B of this response).

You also argue that the Ribavirin Response Letter supports your request in this Petition. The ribavirin petition requested that FDA refrain from approving ANDAs that do not include labeling information on the use of ribavirin with the drug PEG-Intron (peginterferon alfa-2b). The Agency determined that omission of information on the use of ribavirin with PEG-Intron would not render the drug less safe or effective. You state that FDA concluded that the PEG-Intron information could be omitted from the labeling because the generic ribavirin products would still be labeled for combination use with another related product from the same family of drugs as PEG-Intron (Intron A). You argue that FDA should not allow a carve-out of the metformin information from the generic repaglinide labeling because metformin is not chemically or pharmacologically related to any other class of antihyperglycemic agents, including TZDs (Petition at 13). You suggest that because metformin and TZDs are not in the same class of drugs, omission of the metformin information would be confusing and affect the safety and efficacy of the drug product (Petition at 14).

Although it is true that the ribavirin example involved a carve-out of a combination therapy product (PEG-Intron) that is in the same class of drugs as the remaining combination product (Intron A), FDA based its decision to allow a carve out of the PEG-Intron combination therapy information on the fact that the generic ribavirin labeling would be the same as the innovator product labeling for the adult use of ribavirin in combination with Intron A. When FDA approved the NDA for ribavirin, it determined that the drug product was safe and effective for the use in combination with Intron A; and the product was required to have adequate directions for the adult use of ribavirin in combination with Intron A. Therefore, FDA concluded that a generic ribavirin product (with labeling that excludes the information on the use of ribavirin in combination with PEG-Intron) would still be as safe and effective as the innovator product for the adult use of ribavirin in combination with Intron A. Similarly, FDA approved the combination use of repaglinide with metformin and with TZDs based on data derived from separate clinical trials. As such, the repaglinide product labeling contains separate information for each of the combination therapy products. As discussed in section II.B above, FDA has

decided that generic repaglinide, with labeling that carves out the information on use with metformin, will be safe and effective for its remaining conditions of use.

Finally, you suggest that the citizen petition for tramadol[22] supports your argument that generic versions of repaglinide should not be permitted to carve out from the labeling the information on the combination therapy use with metformin. The tramadol petition involved labeling that omitted a protected slower titration schedule for the drug product. You argue that tramadol differs from repaglinide because the unprotected titration information that remained in the generic labeling served the same purpose as the protected, omitted titration information (Petition at 14). You argue that there is no similar unprotected labeling for a repaglinide product.

In the Tramadol Response Letter, FDA allowed information related to a 25-mg, 16-day titration dosing schedule that was protected by 3 years of marketing exclusivity and pediatric exclusivity to be carved out of the generic labeling. The protected dosing schedule was allowed to be carved out of the ANDA labeling because the unprotected 50-mg, 10-day titration dosing schedule provided adequate information. Similarly, we are allowing a carve-out of the metformin information because that information was derived from a separate clinical trial than the information regarding monotherapy or the combination use with TZDs. Therefore, repaglinide will contain sufficient information in the labeling to remain safe and effective for the remaining conditions of use.

E. Generic Versions of Prandin Without Combination-Use Information in the Labeling Are Not Considered New Drugs.

You state that the approval of an ANDA for repaglinide without the metformin information is not permitted because repaglinide has never been approved exclusively as a monotherapy and has always been concurrently approved for combination use with metformin (Petition at 14). It is correct that Prandin has never been approved as monotherapy only. Prandin was approved originally for both monotherapy and combination therapy with metformin, and later for combination therapy with a TZD. It is important to note, however, that each of these uses was derived from separate clinical trials. Information about the efficacy and safety of repaglinide monotherapy or repaglinide with a TZD will be retained after carve-out of the information about metformin.

As noted in section II.A and II. B above, all oral antidiabetic drugs now have the simplified indication: "Drug X is indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus." Therefore, generic versions of repaglinide will contain this same indication because there is no mention of combination use with metformin in the INDICATIONS AND USAGE section of the product labeling. Removing the information in the repaglinide labeling relating to the combination use with metformin does not create a new drug not approved by FDA, because the INDICATIONS

[22] See the June 11, 2002, letter from Janet Woodcock, Director, Center for Drug Evaluation and Research, to Ms. Macdonald, Ms. Jaskot, and Mr. Hurst, Docket Nos. 2001P-0495, 2002P-0191, and 2002P-0252 (Tramadol Response Letter).

AND USAGE section will be the same and the monotherapy and combination uses were derived from different clinical trials. As mentioned in section II.B, we have determined that a carve-out of the metformin information from the drug product labeling will not compromise safety or effectiveness for the remaining, nonprotected conditions of use, which is the standard for evaluating a carve-out situation for generic drug products.

III. ANALYSIS OF THE CARACO PETITION

In the Caraco Petition, the petitioner requests that FDA require any ANDAs for repaglinide that include a section viii statement for claim 4 of the '358 patent (method-of-use claim for combination therapy with metformin) also include a paragraph IV certification to address claims 1-3 and 5 of the '358 patent (Caraco Petition at 2). You claim that FDA cannot approve an ANDA for repaglinide based solely on a section viii statement with regard to the '358 patent because that statement can only address claim 4 (Caraco Petition at 2). Specifically, you state that both the Act and FDA regulations provide that a section viii statement is applicable only to patent claims that describe a method of use (Caraco Petition at 2). You state that claim 4 of the '358 patent is the only claim for a method of use and that claims 1-3 and claim 5 either describe the drug composition of the product or a kit for the treatment of type 2 diabetes (Caraco Petition at 3). Therefore, you argue that ANDAs for repaglinide must submit a paragraph IV certification for claims 1-3 and 5.

We agree that the '358 patent is listed as a drug substance, a drug product, and a method-of-use patent, and are granting your request. The Act and FDA regulations allow a section viii statement only for patent claims that describe a method of use, and the section viii statement would be inapplicable to other patent claims, such as the pharmaceutical composition of a drug product. For drug composition claims, an ANDA applicant would be required to submit the appropriate certification under section 505(j)(2)(A)(vii) of the Act. With respect to repaglinide, an ANDA applicant could not submit a section viii statement for claims 1-3 and 5 of the '358 patent because they do not involve method-of-use claims. Therefore, if an ANDA applicant chooses to submit an application with a section viii statement with respect to claim 4 of the '358 patent, the applicant would also need to submit a paragraph IV certification for claims 1-3 and 5.

IV. CONCLUSION

We have reviewed the petitions and other relevant information available to us. For the reasons stated above, we deny the Novo Nordisk Petition requesting that FDA refrain from approving any ANDAs for a repaglinide product that omits information on metformin combination therapy. With respect to the Caraco Petition, we are granting the request to require any ANDA for repaglinide that includes only a section viii statement with respect to claim 4 of the '358 patent also include a paragraph IV certification for claims 1-3 and 5.

Sincerely,

Janet Woodcock, M.D.
Director
Center for Drug Evaluation and Research